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| EXAMINER | |
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| DUNSTON, JENNIFER ANN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |
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| 11/10/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/091,177 | COME ET AL. | |
| | Examiner | Art Unit | |
| | Jennifer Dunston, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-37,39,40,42-63 and 65* is/are pending in the application.

4a) Of the above claim(s) *1-27,47,56-62 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-37,39,40,42-46,48-55 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This action is in response to the Amendment filed 8/7/2008. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

### *Election/Restrictions*

Applicant elected Group IV with traverse in the reply filed on 7/20/2005.

Claims 1-27, 47, 56-62 and 65 are withdrawn from consideration as being drawn to a non-elected invention. Applicant timely traversed the restriction (election) requirement in the replies filed on 7/20/2005 and 10/3/2005.

This application contains claims 1-27, 47, 56-62 and 65 drawn to an invention nonelected with traverse in the replies filed on 7/20/2005 and 10/3/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 28-37, 39-40, 42-46, 48-55 and 63 are currently under consideration.

### *Information Disclosure Statement*

Receipt of an information disclosure statement, filed on 8/11/2008, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-34, 36, 46, 48, 49 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (WO 00/07018, of record; see the entire reference) in view of Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998, of record; see the entire reference). This rejection was made in the Office action mailed 2/7/2008 and is reiterated below.

Mehta et al teach a three-hybrid method for identifying targets such as proteins of biologically active small molecules, where multiple proteins are screened for interactions with any small ligand (e.g., Abstract; page 3, line 19 to page 4, line 2). The method comprises the steps of (i) providing a hybrid ligand that consists essentially of ligand A and ligand B that are linked together, (ii) introducing the hybrid ligand into a sample containing a first expression vector, including DNA encoding the target for ligand A linked to a coding sequence for a first

transcriptional module for expression as a first hybrid protein; a second expression vector including sequence from a DNA fragment encoding a polypeptide fused to a second transcriptional module for expression as a second hybrid protein; and a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins, (iii) allowing the hybrid molecule to bind to the first hybrid protein through ligand A and to the second hybrid protein through ligand B so as to active the expression of the reporter gene, (iv) identifying samples expressing the reporter gene and characterizing the DNA fragment of the second hybrid protein to determine the protein to which the small molecule is capable of binding (e.g., page 4, lines 3-18; page 25, lines 12-26). The sample environment may be a eukaryotic cell or prokaryotic cell population (e.g., page 7, lines 12-15 and lines 21-29; page 15, lines 1-15). Mehta et al teach that the hybrid ligand may be introduced into the cell by electroporation or any permeation procedure that is known in the art (e.g., page 15, lines 16-18). Mehta et al teach the screening of DNA sequences from a genomic DNA library, cDNA library or synthetically generated library formed from eukaryotic cells, prokaryotic cells, viruses or formed by automated DNA synthesizer (e.g., paragraph bridging pages 16-17). Mehta et al teach the method where the first ligand (ligand A, or R1 of the claims) binds to the ligand binding domain P1 with high affinity and has a dissociation constant ($K_D$) of less than 1 μM (e.g., page 17, lines 17-27). Mehta et al teach that ligand A forms a covalent bond with its target and can be a modified aspirin, beta-lactam antibiotic or a mechanism-based enzyme inactivator that binds to the active site of an enzyme and forms a covalent bond with the enzyme (e.g., page 9, lines 13-17; paragraph bridging pages 10-11). The mechanism-based enzyme inactivator compounds inhibit the enzymes listed in Table 2, which includes Protein

Kinase C (e.g., page 11, lines 8-11; Table 2). Mehta et al teach the method where ligand A and ligand B are not the same (e.g., page 14, lines 16-18). Further, R2 may be selected from a library of variants (e.g., page14, lines 9-15). Mehta et al teach the method where the first hybrid protein comprises a DNA binding domain and the second hybrid protein comprises an activation domain (e.g., page 23, line 5 to page 24, line 18; page 26, lines 1-24). Mehta et al teach the method where the reporter gene is green fluorescent protein or LacZ, which codes for beta-galactosidase (e.g., page 17, lines 8-16). Mehta et al teach the confirmation of the dependence of yeast three hybrid ligand interactions on the presence of both fusion proteins and the hybrid ligand by placing yeast cells in a well of a 96 well plate with hybrid ligand only or no hybrid molecule to serve as controls in the assay (e.g. Example 4). Further, Mehta et al teach the screening of libraries to identify numerous proteins that may interact with the hybrid ligand and teach the confirmation of the interactions using the 96-well microtiter assay (e.g. Example 1). Mehta et al teach that ligand A and ligand B may be linked by any linker known in the art (e.g., page 14, lines 19-25). Mehta exemplifies the use of a linker that is a carbon chain of seven carbon atoms (e.g., Figure 4).

Mehta et al do not teach the method where the linker of the hybrid ligand comprising ligand A (R1) and ligand B (R2) has the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n is an integer from 2 to 5. Mehta et al does not specifically teach that the microtiter plate growth assay is individually conducted on greater than about 10 different positive ligand-binding cell-types identified in the assay.

Keenan et al teach a method comprising the steps of (i) providing a hybrid ligand such as dimerized FK1012 derivative linked by polyethylene linkers, (ii) introducing the hybrid ligand

into a population of cells containing a SEAP reporter gene operably linked to ZFHD1 binding sequences, a first chimeric gene encoding a fusion protein containing three FKBP binding domains and a DNA binding domain from ZFHD1, and a second chimeric gene encoding a fusion polypeptide containing three FKBP binding domains and a transcription activation domain from the NF-κB p65 subunit, and (iii) allowing the hybrid ligand to bind the FKBP binding domains to induce dimerization such that transcription of the SEAP reporter gene is increased, and (iv) identifying positive ligand binding cells by activation of SEAP (e.g. page 1334, Assay for inducible transcriptional activation; Figure 3; Table 1). Keenan et al teach that dimers comprising three or four polyethylene glycol units induced transcriptional activation with potencies only 10- to 20-fold lower than the reference compound 1d (e.g., paragraph bridging pages 1313-1314; Table 1). Thus, Keenan et al teach that the substitution of a 10 atom bisamide linker can be functionally replaced by a polyethylene glycol linker of 3 or 4 units. Increasing the polyethylene glycol units to 5 units results in a decrease in activity to 25% of the reference compound comprising the bisamide linker (e.g., paragraph bridging pages 1313-1314; Table 1).

Because both Mehta et al and Keenan et al teach methods of using a hybrid ligand to activate gene expression in a cell, and because Mehta et al teach it is within the skill of the art to use any known linker to link ligand A and ligand B, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the PEG linker of 3 or 4 units of Kennan et al for the hydrocarbon linker of Mehta et al. Because both linkers have the serve the same purpose and are of about the same length, one would reasonably expect to achieve the predictable result of providing a hybrid ligand capable of functioning in the context of the claimed assay, where the linker is of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n is an integer of 3

or 4. Further, it would have been obvious to conduct the assay on greater than 10 ligand-binding cell types because the assay can result in the identification of at least 10 ligand-binding cell types or can be repeated at least 10 times to identify 10 ligand-binding cell types. One would have been motivated to make such a modification in order to receive the expected benefit of confirming each interaction identified in the screen.

Claims 28-34, 36, 46, 48, 49 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (WO 00/07018, of record; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference). This rejection was made in the Office action mailed 2/7/2008 and is reiterated below.

Mehta et al teach a three-hybrid method for identifying targets such as proteins of biologically active small molecules, where multiple proteins are screened for interactions with any small ligand (e.g., Abstract; page 3, line 19 to page 4, line 2). The method comprises the steps of (i) providing a hybrid ligand that consists essentially of ligand A and ligand B that are linked together, (ii) introducing the hybrid ligand into a sample containing a first expression vector, including DNA encoding the target for ligand A linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein; a second expression vector including sequence from a DNA fragment encoding a polypeptide fused to a second transcriptional module for expression as a second hybrid protein; and a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins, (iii) allowing the hybrid molecule to bind to the first hybrid

protein through ligand A and to the second hybrid protein through ligand B so as to active the expression of the reporter gene, (iv) identifying samples expressing the reporter gene and characterizing the DNA fragment of the second hybrid protein to determine the protein to which the small molecule is capable of binding (e.g., page 4, lines 3-18; page 25, lines 12-26). The sample environment may be a eukaryotic cell or prokaryotic cell population (e.g., page 7, lines 12-15 and lines 21-29; page 15, lines 1-15). Mehta et al teach that the hybrid ligand may be introduced into the cell by electroporation or any permeation procedure that is known in the art (e.g., page 15, lines 16-18). Mehta et al teach the screening of DNA sequences from a genomic DNA library, cDNA library or synthetically generated library formed from eukaryotic cells, prokaryotic cells, viruses or formed by automated DNA synthesizer (e.g., paragraph bridging pages 16-17). Mehta et al teach the method where the first ligand (ligand A, or R1 of the claims) binds to the ligand binding domain P1 with high affinity and has a dissociation constant ($K_D$) of less than 1 μM (e.g., page 17, lines 17-27). Mehta et al teach that ligand A forms a covalent bond with its target and can be a modified aspirin, beta-lactam antibiotic or a mechanism-based enzyme inactivator that binds to the active site of an enzyme and forms a covalent bond with the enzyme (e.g., page 9, lines 13-17; paragraph bridging pages 10-11). The mechanism-based enzyme inactivator compounds inhibit the enzymes listed in Table 2, which includes Protein Kinase C (e.g., page 11, lines 8-11; Table 2). Mehta et al teach the method where ligand A and ligand B are not the same (e.g., page 14, lines 16-18). Further, R2 may be selected from a library of variants (e.g., page14, lines 9-15). Mehta et al teach the method where the first hybrid protein comprises a DNA binding domain and the second hybrid protein comprises an activation domain (e.g., page 23, line 5 to page 24, line 18; page 26, lines 1-24). Mehta et al teach the method

where the reporter gene is green fluorescent protein or LacZ, which codes for beta-galactosidase (e.g., page 17, lines 8-16). Mehta et al teach the confirmation of the dependence of yeast three hybrid ligand interactions on the presence of both fusion proteins and the hybrid ligand by placing yeast cells in a well of a 96 well plate with hybrid ligand only or no hybrid molecule to serve as controls in the assay (e.g. Example 4). Further, Mehta et al teach the screening of libraries to identify numerous proteins that may interact with the hybrid ligand and teach the confirmation of the interactions using the 96-well microtiter assay (e.g. Example 1). Mehta et al teach that ligand A and ligand B may be linked by any linker known in the art (e.g., page 14, lines 19-25). Mehta exemplifies the use of a linker that is a carbon chain of seven carbon atoms (e.g., Figure 4).

Mehta et al do not teach the method where the linker of the hybrid ligand comprising ligand A (R1) and ligand B (R2) has the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n is an integer from 2 to 5. Mehta et al does not specifically teach that the microtiter plate growth assay is individually conducted on greater than about 10 different positive ligand-binding cell-types identified in the assay.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure

contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluorescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the linker of the hybrid ligand of Mehta et al with the linker taught by Bertozzi et al, because both references teach the use of a linker to link two moieties. Thus, it would have been obvious to one skilled in the art to substitute one linker for another to achieve the predictable result of linking the two moieties for use in the screening assay. Further, it would have been obvious to conduct the assay on greater than 10 ligand-binding cell types because the assay can result in the identification of at least 10 ligand-binding cell types or can be repeated at least 10 times to identify 10 ligand-binding cell types. One would have been motivated to make such a modification in order to receive the expected benefit of confirming each interaction identified in the screen. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson et al (US Patent No. 5,585,245, cited as reference P04 on the IDS filed 4/26/2003; see the entire

reference) in view of Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996, cited in a prior action; see the entire reference) and Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference), as evidenced by Varshavsky et al (PNAS, USA, Vol. 93, pages 12142-12149, 1996, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

Johnsson et al teach a method of identifying the binding between a predetermined member of a specific-binding pair and a previously unidentified member of the specific-binding pair, comprising the steps of (i) providing a first DNA-based expression vector containing an expression cassette encoding a C-terminal subdomain of ubiquitin fused in frame to DNA encoding P1 and to a reporter moiety if P1 does not double as a reporter, (ii) providing a second DNA-based expression vector containing an expression cassette encoding randomly generated genomic or cDNA fragments fused to DNA (P2) encoding the N-terminal subdomain of ubiquitin (Nux), (iii) co-transforming a eukaryotic host cell with the first and second vectors such that the fusion proteins are produced, (iv) detecting cleavage of the fusion protein by the reconstituted ubiquitin moiety (e.g. column 9, lines 28-39; column 12, line 12 to column 13, line 20). Johnsson et al teach the method where the ubiquitin is reconstituted by the interaction of a ligand with P1 and P2 (e.g., Figure 5). Further, Johnsson et al teach that the C-terminal subdomain must bear an amino acid extension (i.e., to form Cub-Z) (e.g. column 6, lines 24-26). Thus, the first expressed fusion protein comprises segments P1, Cub-Z and RM, in an order where Cub-Z is closer to the N-terminus than RM (e.g. column 6, lines 24-26; column 12, line 12 to column 13, line 20; Figure 1D). Johnsson et al teach that the arrangement can also be reversed

to have the randomly generated fragment fused to the C-terminal ubiquitin subdomain rather than the N-terminal subdomain (e.g. column 13, lines 15-20). Johnsson et al teach that the system may be used with transmembrane proteins (e.g. column 20, lines 34-45).

Varshavsky is cited only to show that N-end rule degradation operates in all organisms examined, from mammals to fungi and bacteria (e.g. Abstract; page 12147, left column, 1st full paragraph). Thus, the eukaryotic cells taught by Johnsson et al have an N-end rule degradation system.

Johnsson et al do not teach the step of providing a hybrid ligand represented by the general formula R1-Y-R2, wherein Y is a linker with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5.

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of Dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). A first hybrid protein comprising a DNA-binding domain and receptor for Dexamethasone (P1) was provided, and a second hybrid ligand comprising a potential receptor for FK506 (P2) and a transactivation domain was provided (e.g. Figures 2-4). Licitra et al teach the identification of positive interactions using the LacZ reporter gene (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph). Further, Licitra et al suggest the use of other two- and three-hybrid systems that

would allow the utility of the system to be expanded to other types of proteins such as membrane proteins (e.g. page 12820, right column, 1st full paragraph).

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluorescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the two-hybrid method of Johnsson et al to include the hybrid ligand, P1 and P2 portions taught by Licitra et al because Licitra suggest the use of other two- or three-hybrid systems to expand the utility of the assay comprising the hybrid ligand and Johnsson et al teaches a version of a three-hybrid method. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the linker of the hybrid

ligand of Licitra et al with the linker taught by Bertozzi et al, because both references teach the use of a linker to link two moieties. Thus, it would have been obvious to one skilled in the art to substitute one linker for another to achieve the predictable result of linking the two moieties for use in the screening assay.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to identify membrane proteins capable of interacting with FK506 as suggested by Licitra and as taught by Johnsson et al. This modification would expand the utility of the hybrid ligand screening assay. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

Liu et al teach a screening assay for identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand having the general formula A-L-B (or R1-L-R2), where A is a first ligand and B is a user-specified ligand different from A, (ii) introducing the hybrid ligand into a sample containing a functional transcriptional and translational apparatus (for example, a whole cell) that includes vectors a encoding a hybrid protein including a transcription module and a target module for binding ligand A (P1) or for

binding ligand B (P2) (target proteins #1 and #2), (iii) once the three hybrid complex comprising the hybrid ligand, first fusion protein and second fusion protein is formed, transcriptional activation of a reporter gene occurs, and (iv) retrieving the plasmid encoding the fusion protein capable of binding to B and sequencing the plasmid (e.g. column 5. line 55 to column 8, line 46; column 11, lines 25-32; Figure 2). Liu et al teach that one of the vectors capable of binding the ligand contains a DNA binding domain and the other contains a transcription activation domain (e.g. column 7, lines 24-59; Figures 1-3). Liu et al teach that the nucleic acid sequence encoding the ligand B binding domain polypeptide is from random DNA sequences of a size that is capable of encoding a yet undetermined target protein, where the random sequences are derived from a genomic DNA library, cDNA library or synthetically generated library formed from eukaryotic cells, prokaryotic cells, viruses, or formed by an automated DNA synthesizer (e.g. paragraph bridging columns 7-8). With regard to the affinity of the hybrid ligand A to P1, Liu et al teach binding affinities including a Kd below $10^{-6}$, $10^{-7}$, $10^{-8}$ or $10^{-9}$ (e.g. column 8, lines 31-46). Liu et al teach that ligand A may be selected based upon a strong binding affinity for a target encoded by a fusion gene; the binding affinity must necessarily be measured if this determination is made (e.g. column 8, lines 31-46). Liu et al teach that A may form a covalent bond with P1 if a suicide inhibitor is used, for example beta-lactamase as P1 can covalently bind suicide inhibitors used as ligand A, including beta-lactam antibiotics (e.g. paragraph bridging columns 5-6). With regard to the reporter gene, Liu et al teach the use of LacZ, and GFP (e.g. column 8, lines 17-30; Figures 1-3). With regard to ligand B, Liu et al teach that the ligand may be selected from FK506, peptide libraries, nucleic acid libraries, polysaccharide libraries, and small organic molecules (e.g. column 6, lines 14-26). Liu et al teach the use of control

experiments containing hybrid ligand only (without target proteins #1 and #2) to determine if the effects of the hybrid ligand are independent of trimeric complex formation (e.g. Example 5). Liu et al teach the use of control experiments to confirm that reporter gene activation does not occur in the presence of the two target proteins in the absence of the hybrid ligand (e.g. column 11, lines 11-32). Liu et al teach that ligand A and ligand B may be covalently linked by any of the methods known in the art (e.g. column 6, lines 27-37).

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-36, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and supporting pages S1-S12, published online 4/13/2000, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the three-hybrid method where A (or R1) is methotrexate.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Lin et al teach a method of identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand comprising methotrexate linked to dexamethasone through a linker region, (ii) introducing the hybrid ligand into yeast cells comprising a LacZ reporter gene operably linked to a LexA binding site, a first chimeric gene encoding a fusion polypeptide of LexA and DHFR, a second chimeric gene encoding a fusion protein of GR and B42, (iii) allowing the hybrid ligand to bind the first and second fusion proteins to result in an increase in the level of the transcription of the reporter gene, (iv) identifying a positive ligand binding cell by detecting blue colonies of yeast grown on X-gal

containing plates, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 4248, left column; Figures 1 and 2; Scheme 1; page S6). Further, Lin et al teach the assay where one of the fusion proteins is deleted to detect the effect of the hybrid ligand independent of the formation of the trimeric complex of the two fusion proteins and the hybrid ligand (e.g. page 4248, left column, last paragraph). Moreover, Lin et al teach the assay in the absence of the hybrid ligand to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand and fusion proteins (e.g. Figure 2). Lin et al teach that methotrexate can be modified readily without disrupting receptor binding, is commercially available, and has a picomolar affinity for DHFR (e.g. page 4247, right column, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious at the time the invention was made to modify the hybrid ligand of Liu et al to include methotrexate as A (or R1), because Liu et al teach that A can be varied and Lin et al teach the use of methotrexate in a three-hybrid assay.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use methotrexate as R1, because Lin et al teach that methotrexate can be modified readily without disrupting receptor binding, is commercially available, and has a picomolar affinity for DHFR. Based upon the teachings of the cited references, the high skill of

one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Karlsson et al (US Patent No. 6,143,574, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the use of plasmon resonance to determine the binding affinity of A to a fusion protein.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for

conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Karlsson et al teach that the BIAcore instrument uses the phenomenon of surface plasmon resonance to study the binding of analytes to receptors immobilized on a sensor chip to allow the affinity and kinetic analysis of interactions between soluble analytes and their immobilized binding partners to be determined (e.g. column 1, lines 11-45). Karlsson et al teach that affinity and kinetic properties for the solution interaction between an analyte and a binding partner can be determined by the following steps: (i) mixing the analyte with an immobilized binding partner (e.g. column 2, lines 3-15; column 3, lines 17-20). Karlsson et al teach that the method provides the ability to not only determine the true affinity properties but also true kinetic properties for the solution interaction between an analyte and binding partner therefore to thereby among other things be permitted a wider choice of reaction partners than in solid phase interactions and avoid immobilization artifacts (e.g. column 1, lines 59-65).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious at the time the invention was made to include the use of plasmon

resonance to determine the binding affinity of A to P1, because Liu et al teach it is within the skill of the art to select A and P1 based upon binding affinity and Karlsson et al teach a method of determining binding affinity using plasmon resonance.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use the plasmon resonance method of Karlsson et al in order to receive the expected benefit of providing the ability to not only determine the true affinity properties but also true kinetic properties for the solution interaction between an analyte and binding partner therefore to thereby among other things be permitted a wider choice of reaction partners than in solid phase interactions and avoid immobilization artifacts. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52, 53 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the step of providing access to data, nucleic acids or peptides obtained from the identification of polypeptide binding to a hybrid ligand.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of Dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). Licitra et al teach the identification of positive interactions using the LacZ reporter gene and disclose the data in the publication (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages

over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious to provide the public access to the data through publication as taught by Licitra et al, because Liu et al teach a three-hybrid assay and Licitra teach a three-hybrid assay and provide the data obtained from the assay.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. One would have been motivated to publish the data obtained from such an assay to be able to communicate the findings to peers in the form of a publication. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36-37, 39-40, 42, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited

as reference CC on the IDS filed 7/20/2005; see the entire reference) and Zaharevitz et al (Cancer Research, Vol. 59, pages 2566-2569, cited in a prior action, 1999; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

The teachings of Liu et al are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the method where ligand B is a cyclin dependent kinase inhibitor of Table 2.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Zaharevitz et al teach a small molecule cyclin dependent kinase inhibitor found on page 1 of instant Table 2 (e.g. Figures 1 and 4). Zaharevitz et al teach that these compounds are novel and are able to interact with a subset of CDKs (e.g. paragraph bridging pages 2568-2569). Further, Zaharevitz et al teach that the disclosed compounds are useful as a tool for exploring the structural bases and pharmacological significance of various kinase specificites.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the CDK inhibitors disclosed by Zaharevitz et al as ligand B, because Liu et al teach that ligand B may be selected from a small molecule library and Zaharevitz et al teach that the kinase inhibitor is a small molecule.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use the kinase inhibitors of Zaharevitz et al as ligand B to be able to screen for other kinases capable of binding the inhibitors to further characterize the kinase specificities of the inhibitors. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868, cited in a prior action; see the entire reference) in view of Holt et al (WO 96/06097, cited as reference AD on the IDS filed 4/28/2003; see the entire reference). This rejection was made in the Office action mailed 10/18/2007 and is reiterated below.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5.

Holt et al teach the formation of heterodimers of immunophilin ligand moieties (e.g. FK506 and derivatives thereof) (e.g. page 1; page 6, lines 12-17). Holt et al exemplify structures linked by polyethylene linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 1, 2, 3, 4 (e.g. pages 14-15). Holt et al teach the use of the homodimeric ligands comprising the abovementioned linker where n = 2 or 3 in an cell-based transfection assay where a trimeric complex comprising the homodimeric ligand, a fusion protein comprising three copies of FKBP12 fused to a Gal4 DNA binding domain, and a fusion protein comprising three copies of FKBP12 fused to a VP16 activation domain was detected by the production of the reporter product, secreted alkaline phosphatase (e.g. pages 48-49). Holt et al teach that multimerizers vary somewhat in their observed activity, depending upon the particular chimeric proteins and other components of the system and recommend that the practitioner select multimerizers based upon their performance in the particular system of interest (e.g. page 48 lines 26-30).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand in the three-hybrid assay to include the $(CH_2\text{-}O\text{-}CH_2)_n$ linker of Holt et al because Liu et al teach it is within the ordinary skill in the art to use any linker known in the art and Holt et al teach linkers for making homodimeric or heterodimeric ligands capable of forming a trimeric complex in three hybrid assay.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to vary the linker of the hybrid ligand to determine which ligand performs best in the three-hybrid system as taught by Holt et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

***Response to Arguments - 35 USC § 103***

With respect to the rejection of claims 28-34, 36, 46, 48, 49 and 52-55 under 35 U.S.C. 103(a) as being unpatentable over Mehta in view of Keenan et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Keenan et al fails to teach a screening method to identify a polypeptide that binds to a user-specified ligand, as recited in claim 28. Further, the response asserts that Keenan et al never teach or suggest a candidate ligand-binding domain P2 as in step (ii)(c) of claim 28, since both ligand-binding domains taught in Keenan et al are already known and invariable. The response asserts that Keenan et al fail to teach screening a library of nucleic

acid sequences encoding P2. Moreover, the response asserts that Keenen et al fail to teach the screening step (v) of claim 28 as they do not perform any actual screening.

These arguments are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection of record is based upon the combined teachings of Mehta et al and Keenan et al. Mehta et al teach a three-hybrid method for identifying targets such as proteins of biologically active small molecules, where multiple proteins are screened for interactions with any user defined small ligand (e.g., Abstract; page 3, line 19 to page 4, line 2). The teachings of Mehta et al meet each of the limitations of the rejected claims, except Mehta et al do not teach the method where the linker of the hybrid ligand comprises $(CH_2\text{-}O\text{-}CH_2)_n$, where n is an integer from 2 to 5 and do not teach that the microtiter plate growth assay is individually conducted on greater than bout 10 different positive ligand-binding cell types identified in the assay. Keenan et al teach the claimed linker in the context of a hybrid molecule used in a three-hybrid assay. Both Mehta et al and Keenan et al teach methods where a hybrid ligand is used to activate gene expression in the context of a three-hybrid ligand. The combined teachings of the references meet each of the limitations of the rejected claims for the reasons set forth on pages 3-7 of the Office action mailed 2/7/2008.

The response asserts that Keenan et al teaches away from peg linkers (e.g., 1q-1r) as recited in claim 28, because the Keenan et al article indicates that the ability of these PEG linkers to "induce apoptosis in the Fas assay was poor" (e.g., page 1313, 2nd column, 2nd full

paragraph). The response notes that Keenan et al teach test compounds modified relative to a reference compound, where the test compounds comprise a polyether linker not present in the reference compound. The response notes that Keenan et al conclude that the three polyether linkers tested in ligand 1p-1r, described as "[a] more radically altered set of compound" (e.g., page 1313, right column), are "poor" in terms of their ability to induce apoptosis. The response notes that the reference linker in 1d has an $IC_{50}$ 50 about 6 nM. In contrast, the best of 1p-1r has an $IC_{50}$ of about 140 nM, about 24 times worse than 1d. Further, the response notes that the sample linkers, 1p-1r are not as effective as 1d in the stable and transient transfection assays, with $EC_{50}$ between 5-20 times lower than that of 1d. Of all the linkers tested all but one, lo, are better than the polyether linkers in both the apoptosis and transient transfection assay.

These arguments are not found persuasive. It is noted that the combined teachings of Mehta et al and Keenan et al are directed to the use of the linkers in a hybrid compound used in three-hybrid assays involving transient transfection. The combined teachings are not directed to apoptosis assays. Keenan et al teach that the PEG linkers have minimal (if any) activity in stable transfection assays (e.g., Table 1). In contrast, Keenan et al state, "In the transient transcription assay, 1o, 1p, and 1q induced transcriptional activation with potencies only 10- to 20-fold lower than 1d while the longer-linked compound 1r was able only to achieve one-fourth the level of expression as 1d." See page 1313, right column, last paragraph. Ligands 1p, 1q and 1r had 85%, 60% and 25% the activity of the reference compound, compound 1d. Thus, these ligands successfully activate transcription in the transient transfection based assay. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d

1130, 1132 (Fed. Cir. 1994). While Keenan et al teach away from using the ligands in a stable transfection assay, the performance of compounds 1p and 1q in the transient transfection assay does not discredit the use of these linkers in the synthesis of a hybrid ligand for transient transfection assays.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 28-34, 36, 46, 48, 49 and 52-55 under 35 U.S.C. 103(a) as being unpatentable over Mehta in view of Bertozzi et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Bertozzi et al teach away from using PEG linkers, because Bertozzi et al disclose the use of PEG linkers in heterodimeric hybrid ligands with increased water solubility (hydrophilicity), as well as the chemistry and synthesis of such ligands. The response asserts that it is well known in the art that biological membranes are highly hydrophobic, and thus, when attempting to provide improved membrane-permeable heterodimeric ligands useful for *in vivo* application, the skilled artisan would not be motivated to search for hydrophobic moieties, rather than hydrophilic moieties. Accordingly, the response asserts that the skilled artisan would be motivated to search for hydrophobic moieties, rather than hydrophilic moieties and would have had no motivation to use ligands incorporating a linker for *in vivo* use.

These arguments are not found persuasive. The claims do not require the hybrid ligand to be membrane permeable. The claims encompass any method of introducing the hybrid ligand into a population of cells. Mehta et al teach delivering the hybrid ligand to the cells by

electroporation or any permeation procedure that is known in the art (e.g., page 15, lines 16-18). The method of delivery of Mehta et al does not rely upon the hydrophobicity of the hybrid ligand. Further, the claims do not require *in vivo* administration of the compound to the cells for screening, and the Mehta et al teach *in vitro* assays in cultured cells. By combining the teachings of Mehta et al and Bertozzi et al, one would not have been concerned with developing hybrid ligands for *in vivo* applications. Thus, the teachings of Mehta et al do not require a hydrophobic ligand, and Bertozzi et al do not teach away from the combination of references.

The response asserts that the present invention discloses the surprising discovery that the use of PEG linkers actually increases the cellular uptake of the hybrid ligands, as shown in Figures 6 and 7 and Example 7 of the present specification. The response asserts that this discovery is surprising in view of the Bertozzi et al teaching and the known water solubility of polyethylene glycols.

Example 7 of the specification provides a side by side comparison of Mtx-mdbt-Dex (Lin et al., J. Am. Chem. Soc. 2000, 122:4247-8) and Mtx-(ethyleneglycol)$_3$-Dex (GPC 285937). Each of the compounds was added to medium into which yeast cells were added. GPC 285937 allowed growth of the yeast cells at a concentration between 25 to 400 μM showing optimum growth at 100 μM. In contrast, Mtx-mdbt-Dex showed severe precipitation in the medium, which was hypothesized to cause the compound to be less bio-available and hence the growth of the yeast cells was impaired relative to GPC 285937 (e.g., page 128). In a halo assay, where 1 μl of a 1 mM solution of GPC 285937 or Mtx-mdbt-Dex dissolved in DMSO was spotted in the center of petri dishes containing yeast cells. The growth halo for yeast cells receiving Mtx-mdbt-Dex was much smaller than that of GPC 285937 (e.g., page 129; Figure 6a and 6b). Under

conditions appropriate to library screening of yeast cell, yeast cells were plated on plates containing 200 μM GPC 285937 or Mtx-mdbt-Dex. Clones visibly grew better on media containing GPC 285937 (e.g., page 129; Figure 7). The specification asserts that CPC 285937 has significantly better solubility and membrane permeability (e.g., page 75, 2nd paragraph).

However, the properties of better solubility and membrane permeability are not unexpected. Harris ("Introduction to Biotechnical and Biomedical Applications of Poly(Ethylene Glycol)." Poly(Ethylene Glycol) Chemistry: Biochemical and Biomedical Applications. Ed. J. Milton Harris. Plenum Press, New York, 1992. 1-14, of record.) teaches that covalently linked PEG will solubilize other molecules and move molecules across cell membranes (e.g., page 3, items #13 and #18).

Even if the results observed in the specification are unexpected, they are not commensurate in scope with the claimed invention. The properties of improved solubility and permeability all relate to the ability to deliver the hybrid ligand to the cell by including the compound in a yeast cell growth medium, either liquid or solid. The claims do not contain a step of adding the hybrid ligand to a medium for the growth of yeast cells. The prior art teaches that hybrid ligands can be delivered to cells by any method known in the art, including methods such as electroporation (Mehta et al, page 15, lines 16-18; Liu et al, column 7, lines 3-15), which are not dependent upon solubility in culture media and membrane permeability of the compound. If the results are unexpected, Applicant has shown only that the linker of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n=3 has improved properties. The claims are drawn to a genus of linkers. For example, Keenan et al (of record) teaches that lengthening the PEG linker results in reduced activity (e.g., $(\text{polyethylene glycol})_3 > (\text{polyethylene glycol})_4 >> (\text{polyethylene glycol})_5$).

Applicant has not demonstrated that linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n=25 would have the proposed unexpected properties. Thus, Applicant has not provided evidence that the unexpected results occur over the entire claimed genus of R1-Y-R2 for the claimed method conditions.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

With respect to the rejection of claims 43-45 under 35 U.S.C. 103(a) as being unpatentable over Johnsson et al in view of Licitra et al and Bertozzi et al, as evidenced by Varashavsky et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Licitra et al teach away from improving the linker in the hybrid ligand, because they suggest generating yeast strains that are more permeable without significantly affecting yeast viability. This is not found persuasive, because improving the invention by generating yeast strains that are more permeable does not preclude one from modifying or optimizing a hybrid ligand for use in the assay. As discussed by Applicant and noted in the prior art (Harris, J. Milton. "Introduction to Biotechnical and Biomedical Applications of Poly(Ethylene Glycol)." Poly(Ethylene Glycol) Chemistry: Biochemical and Biomedical Applications. Ed. J. Milton Harris. Plenum Press, New York, 1992. 1-14, of record. See page 3, item #13) PEG is used to increase the solubility of covalently linked compounds. Thus, one would be motivated to increase the solubility of the compound regardless of any effect the modification may have on membrane permeability.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

With respect to the rejection of claims 28-34, 36, 46, 48-50, 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Bertozzi et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Liu et al describe a cell-based *in vivo* screening method using hybrid ligands. In fact, Liu et al teach the assay in an environment that may be whole cells, cell lysate, or a synthetic mixture of enzymes and reagents (e.g., column 6, lines 50-51). Liu et al provide examples of cellular environments, including a yeast cell population, invertebrate cell lines, and mammalian cells (e.g., column 6, lines 54-58). Liu et al teach that cells capable of use in the three hybrid assay include primary cultures, cultures of immortalized cells or genetically manipulated strains of cells (e.g., column 6, lines 58-61). Accordingly, the teachings of Liu et al are directed to the use of cells cultured *in vitro*.

The response asserts that when attempting to provide improved membrane-permeable heterodimeric hybrid ligands for *in vivo* applications, such as the screening assay disclosed in Liu et al, a skilled artisan would be motivated to look for hydrophobic moieties, rather than hydrophilic moieties, such as PEG linkers disclosed in Bertozzi et al. The response asserts that the skilled artisan would have had no motivation to use ligands incorporating such a linker for *in vivo* use, because PEG linkers are known to be hydrophilic, and therefore would be expected to decrease membrane permeability of the ligand. Further, the response asserts that even if the PEG linker provided some benefit to link moieties A and B of the hybrid ligand of Liu et al, such a

benefit would be outweighed by the paramount importance of membrane permeability required of such a hybrid ligand.

These arguments are not found persuasive. The claims do not require the hybrid ligand to be membrane permeable. The claims encompass any method of introducing the hybrid ligand into a population of cells. Furthermore, Liu et al teach the following with regard to the linker:

> The covalent hybrid linkage between ligand A and ligand B may be formed by any of the methods known in the art. (for example: Jerry March, Advanced Organic Chemistry (1985) Pub. John Wiley & Sons Inc; and HH, House, Modern Synthetic Reactions (1972) pub. Benjamin Cummings) Example 1 and FIG. 7 describes an embodiment of a linkage reaction between dexamethasone and FK506. Descriptions of linkage chemistries are further provided by Crabtree et al. WO 94/18317, 95/02684, Schreiber et al WO 96/13613, Holt et al. WO96/06097; these references being incorporated herein by reference.

Liu et al specifically teach using the linkers described by Holt et al (WO 96/06097, of record). Holt et al teach the formation of heterodimers of immunophilin ligand moieties (e.g. FK506 and derivatives thereof) (e.g. page 1; page 6, lines 12-17). Holt et al exemplify structures linked by polyethylene linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 1, 2, 3, 4 (e.g. pages 14-15). Holt et al teach the use of the homodimeric ligands comprising the abovementioned linker where n = 2 or 3 in an cell-based transfection assay where a trimeric complex comprising the homodimeric ligand, a fusion protein comprising three copies of FKBP12 fused to a Gal4 DNA binding domain, and a fusion protein comprising three copies of FKBP12 fused to a VP16 activation domain was detected by the production of the reporter product, secreted alkaline phosphatase (e.g. pages 48-49). Holt et al teach it is within the skill of the art to use these linkers to optimize a particular ligand by routine experimentation. A suggestion or motivation to combine references is an appropriate method for determining obviousness; however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary

rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham. KSR*, 550 U.S. at ___, 82 USPQ2d at 1395-97. See MPEP § 2141 and § 2143. It would have been obvious to substitute one known linker with another known linker in order to achieve the predictable result of linking two ligands for use in the claimed assay (e.g., page 48). Bertozzi et al provide a known method of linking two compounds using a PEG linker. Because Liu et al and Bertozzi et al teach linkers for linking two compounds, it would have been obvious to one skilled in the art to substitute one linker for the other in order to achieve the predictable result of linking two compounds for use in the assay disclosed by Liu et al. Furthermore, Liu et al teach electroporation or any method that is well known in the art to introduce the hybrid ligand into the cell (e.g., column 7, lines 3-7).

The response asserts that the present invention discloses the surprising discovery that the use of PEG linkers in accordance with the teachings disclosed herein actually increases the cellular uptake of the hybrid ligands, as shown in Figures 6 and 7 and Example 7 of the specification.

Example 7 of the specification provides a side by side comparison of Mtx-mdbt-Dex (Lin et al., J. Am. Chem. Soc. 2000, 122:4247-8) and Mtx-(ethyleneglycol)$_3$-Dex (GPC 285937). Each of the compounds was added to medium into which yeast cells were added. GPC 285937 allowed growth of the yeast cells at a concentration between 25 to 400 μM showing optimum growth at 100 μM. In contrast, Mtx-mdbt-Dex showed severe precipitation in the medium, which was hypothesized to cause the compound to be less bio-available and hence the growth of the yeast cells was impaired relative to GPC 285937 (e.g., page 128). In a halo assay, where 1 μl

of a 1 mM solution of GPC 285937 or Mtx-mdbt-Dex dissolved in DMSO was spotted in the center of petri dishes containing yeast cells. The growth halo for yeast cells receiving Mtx-mdbt-Dex was much smaller than that of GPC 285937 (e.g., page 129; Figure 6a and 6b). Under conditions appropriate to library screening of yeast cell, yeast cells were plated on plates containing 200 μM GPC 285937 or Mtx-mdbt-Dex. Clones visibly grew better on media containing GPC 285937 (e.g., page 129; Figure 7). The specification asserts that CPC 285937 has significantly better solubility and membrane permeability (e.g., page 75, 2nd paragraph).

However, the properties of better solubility and membrane permeability are not unexpected. Harris ("Introduction to Biotechnical and Biomedical Applications of Poly(Ethylene Glycol)." Poly(Ethylene Glycol) Chemistry: Biochemical and Biomedical Applications. Ed. J. Milton Harris. Plenum Press, New York, 1992. 1-14, of record.) teaches that covalently linked PEG will solubilize other molecules and move molecules across cell membranes (e.g., page 3, items #13 and #18).

Even if the results observed in the specification are unexpected, they are not commensurate in scope with the claimed invention. The properties of improved solubility and permeability all relate to the ability to deliver the hybrid ligand to the cell by including the compound in a yeast cell growth medium, either liquid or solid. The claims do not contain a step of adding the hybrid ligand to a medium for the growth of yeast cells. The prior art teaches that hybrid ligands can be delivered to cells by any method known in the art, including methods such as electroporation (Liu et al, column 7, lines 5-7), which are not dependent upon solubility in culture media and membrane permeability of the compound. If the results are unexpected, Applicant has shown only that the linker of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n=3 has improved

properties. The claims are drawn to a genus of linkers. For example, Keenan et al (of record) teaches that lengthening the PEG linker results in reduced activity (e.g., (polyethylene glycol)$_3$ > (polyethylene glycol)$_4$ >> (polyethylene glycol)$_5$). Applicant has not demonstrated that linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n=25 would have the proposed unexpected properties. Thus, Applicant has not provided evidence that the unexpected results occur over the entire claimed genus of R1-Y-R2 for the claimed method conditions.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 28-36, 46, 48-50, 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Bertozzi et al and Lin et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Lin et al does not teach a hybrid ligand R1-Y-R2, wherein R2 binds or inhibits a kinase. The response asserts that the Examiner is basing the rejection on the erroneous assumption that methotrexate is a kinase inhibitor.

These arguments are not found persuasive. The rejected claims are not drawn the method where R2 binds or inhibits a kinase. Claim 35 is drawn to the method "wherein R1 is methotrexate, and Y is $(CH_2\text{-}O\text{-}CH_2)_n$, n = 2 to 5." The references teach the method where R1 is methotrexate. Claims 37, 39 and 40, which are drawn to the method where R2 binds to or inhibits a kinase are not included in this rejection.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 28-34, 36, 46 and 48-53 under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Bertozzi et al and Karlsson et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that the arguments presented for combination of Liu and Bertozzi et al are applied to this rejection, and Karlsson et al's teaching of the use of plasmon resonance to determine binding affinity doe not, either alone or in combination with Liu et al and Bertozzi et al render claims 28-34, 36, 46 and 48-53 obvious. These arguments are not found persuasive for the reasons set forth above with regard to the combination of Liu et al and Bertozzi et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 28-34, 36, 46, 48-50, 52, 53 and 63 under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Bertozzi et al and Licitra et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Licitra et al teach away from improving the linker in their hybrid ligand by suggesting that a better approach would be to "generate yeast strains that are more permeable without significantly affecting yeast viability" (page 12820, right column).

This is not found persuasive, because improving the invention by generating yeast strains that are more permeable does not preclude one from modifying or optimizing a hybrid ligand for use in the assay. As discussed by Applicant and noted in the prior art (Harris, J. Milton. "Introduction to Biotechnical and Biomedical Applications of Poly(Ethylene Glycol)." Poly(Ethylene Glycol) Chemistry: Biochemical and Biomedical Applications. Ed. J. Milton Harris. Plenum Press, New York, 1992. 1-14. See page 3, item #13) PEG is used to increase the

solubility of covalently linked compounds. Thus, one would be motivated to increase the solubility of the compound regardless of any effect the modification may have on membrane permeability.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

With respect to the rejection of claims 28-37, 36-37, 39-40, 42, 46, 48-50, 52 and 53 are rejected as being unpatentable over Liu et al in view of Bertozzi et al and Zaharevitz et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response notes that the arguments presented with respect to the rejection over Liu et al in view of Bertozzi et al are applicable to this rejection. The response asserts that the added disclosure of Zaharevitz et al does not render the claims obvious in view of the discussion with regard to Liu et al and Bertozzi et al. These arguments are not found persuasive for the reasons set forth above with respect to the combination of Liu et al and Bertozzi et al.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

With respect to the rejection of claims 28-34, 36, 46, 48-50, 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Holt et al, Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive.

The response asserts that Holt teaches that the linker may be selected from a very broad range of structural types, and does not provide a relevant teaching as to which of the numerous types of linkers are preferred for any reason. This is not found persuasive. Liu et al teach the following with regard to the linker:

> The covalent hybrid linkage between ligand A and ligand B may be formed by any of the methods known in the art. (for example: Jerry March, Advanced Organic Chemistry (1985) Pub. John Wiley & Sons Inc; and HH, House, Modern Synthetic Reactions (1972) pub. Benjamin Cummings) Example 1 and FIG. 7 describes an embodiment of a linkage reaction between dexamethasone and FK506. Descriptions of linkage chemistries are further provided by Crabtree et al. WO 94/18317, 95/02684, Schreiber et al WO 96/13613, Holt et al. WO96/06097; these references being incorporated herein by reference.

Liu et al specifically teach using the linkers described by Holt et al (WO 96/06097, of record). Holt et al disclose species of ligands that meet the structural limitations of the claims. Holt et al teach the formation of heterodimers of immunophilin ligand moieties (e.g. FK506 and derivatives thereof) (e.g. page 1; page 6, lines 12-17). Holt et al exemplify structures linked by polyethylene linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 1, 2, 3, 4 (e.g. pages 14-15). Holt et al teach the use of the homodimeric ligands comprising the abovementioned linker where n = 2 or 3 in an cell-based transfection assay where a trimeric complex comprising the homodimeric ligand, a fusion protein comprising three copies of FKBP12 fused to a Gal4 DNA binding domain, and a fusion protein comprising three copies of FKBP12 fused to a VP16 activation domain was detected by the production of the reporter product, secreted alkaline phosphatase (e.g. pages 48-49). Holt et al teach it is within the skill of the art to use these linkers to optimize a particular ligand by routine experimentation. The response asserts that there is nothing in Holt et al that motivate one skilled in the art to select the subgenus of PEG linkers from the numerous disclosed linkers. A suggestion or motivation to combine references is an appropriate method for determining obviousness; however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham. KSR*, 550 U.S. at ___, 82 USPQ2d at 1395-97. See MPEP § 2141 and §

2143. It would have been obvious to substitute one known linker with another known linker in order to achieve the predictable result of linking two ligands for use in the claimed assay (e.g., page 48). Furthermore, Liu et al specifically teach the use of any linker known in the art, including linkers taught by Holt et al (e.g., column 6, lines 27-37).

The response asserts that Holt et al do not teach that PEG linkers would increase cellular uptake of the hybrid ligands. This is not found persuasive, because the claims do not require cellular uptake of the hybrid ligands.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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